

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1-16. (canceled)

17. (currently amended) A multimeric molecule, ~~characterized in that it corresponds~~ corresponding to the following general formula:



~~in which~~ wherein:

[[-]] n is equal to 3, 4, 5 or 6,

[[-]] A is a chemical ~~group~~ moiety, functionalized by at least three amino functions or COOH functions or SH functions or S-Npys (S-nitro-pyridinesulphenyl) functions or S-Pys (S-pyridinesulphenyl) functions, ~~and is in particular different from a protein,~~

[[-]] X represents a -D, -B-D, or -B(D)-D' group, in which:

[[*]] B is a spacer arm, and

[[*]] -D and -D' each represent ~~peptides or pseudo-peptides~~ a peptide corresponding to a sequence derived from a ligand, chosen from the residues forming the interface with the ligand receptor, ~~which~~ said sequence ~~is~~ capable of interacting with the receptor, said ligand being ~~chosen from the ligands of~~

~~receptors of the TNF superfamily, and in particular from the following ligands: EDA, CD40L, FasL, OX40L, AITRL, CD30L, VEGI, LIGHT, 4-1BBL, CD27L, LT α , TNF, LT β , TWEAK, APRIL, BLYS, RANKL and TRAIL.~~

18. (Currently Amended) The molecule of claim 17, wherein -D and -D' each represent ~~peptides~~ a peptide derived from the ligand of the human or murine CD40 receptor (CD40L), each said ~~peptides~~ peptide belonging to the primary sequence of the CD40L ~~ligand of CD40 and the number of amino acids of which is comprised between 3 and 10~~ comprising between 3 and 10 amino acids.

19. (Currently Amended) The molecule of claim 17, wherein ~~the peptides~~ each peptide derived from the ligand of the human or murine CD40 receptor (CD40L) ~~are~~ is chosen from the following:

Lys[[¹⁴³]]-Gly-Tyr[[¹⁴]] (SEQ ID NO: 1)[[⁵]],

Tyr[[¹⁴⁵]]-Gly-Lys[[¹⁴³]] (SEQ ID NO: 2),

Lys[[¹⁴³]]-Gly-Tyr-Tyr[[¹⁴⁶]] (SEQ ID NO: 3),

Tyr[[¹⁴⁶]]-Tyr-Gly-Lys[[¹⁴³]] (SEQ ID NO: 4),

Lys-Pro-Arg (SEQ ID NO: 5), ~~H-Lys- Ψ (CH₂NH)-Pro-Arg~~
~~(SEQ ID NO: 24),~~

Arg[[²⁰⁰]]-Phe-Glu-Arg-Ile-Leu-Leu-Arg[[²⁰⁷]] (SEQ ID NO: 6),

Arg^{[[207]]}-Leu-Leu-Ile-Arg-Glu-Phe-Arg^{[[200]]} (SEQ ID NO: 7),
Arg^{[[200]]}-Phe-Glu-Arg-Ile^{[[204]]} (SEQ ID NO: 25),
Ile^{[[204]]}-Arg-Glu-Phe-Arg^{[[200]]} (SEQ ID NO: 9),
Arg^{[[203]]}-Ile-Leu-Leu-Arg^{[[207]]} (SEQ ID NO: 10),
Arg^{[[207]]}-Leu-Leu-Ile-Arg^{[[203]]} (SEQ ID NO: 11),
Cys^{[[218]]}-Gly-Gln-Gln-Ser-Ile^{[[223]]} (SEQ ID NO: 12),
Ile^{[[223]]}-Ser-Gln-Gln-Gly-Cys^{[[218]]} (SEQ ID NO: 26),
Gly^{[[200]]}-Ser-Glu-Arg-Ile-Leu-Leu-Lys^{[[207]]} (SEQ ID NO: 14),
Lys^{[[207]]}-Leu-Leu-Ile-Arg-Glu-Ser-Gly^{[[200]]} (SEQ ID NO: 15),
Gly^{[[200]]}-Ser-Glu-Arg-Ile^{[[204]]} (SEQ ID NO: 16),
Ile^{[[204]]}-Arg-Glu-Ser-Gly^{[[200]]} (SEQ ID NO: 17),
Arg^{[[203]]}-Ile-Leu-Leu-Lys^{[[207]]} (SEQ ID NO: 18),
Lys^{[[207]]}-Leu-Leu-Ile-Arg^{[[203]]} (SEQ ID NO: 19),
Cys^{[[218]]}-Glu-Gln-Gln-Ser-Val^{[[223]]} (SEQ ID NO: 20),
Val^{[[223]]}-Ser-Gln-Gln-Glu-Cys^{[[218]]} (SEQ ID NO: 21),

or from hybrid peptides constituted by at least two consecutive amino acids of two of the sequences defined above, ~~in particular the peptides with the sequences Arg²⁰³-Ile²⁰⁴-Tyr¹⁴⁵-Tyr¹⁴⁶- (SEQ ID NO: 22) or Arg²⁰³-Ile²⁰⁴-Tyr¹⁴⁶-Tyr¹⁴⁵-Gly¹⁴⁴-Lys¹⁴³- (SEQ ID NO: 23),~~ or from fragments of ~~the abovementioned sequences~~ said peptides and hybrid peptides, the amino acids being equally able to be of L or D-configuration.

20. (Previously Presented) The molecule of claim 17, wherein A has a C₃ symmetry.

21. (Currently Amended) The molecule of claim 17, wherein:

[[•]] either A is a branched radical with C₃ symmetry with the following general formula:

$$Y-\left[\left(\text{CH}_2\right)_m-Z-\left(\text{CH}_2\right)_{m'}-V-\right]_3$$

in which:

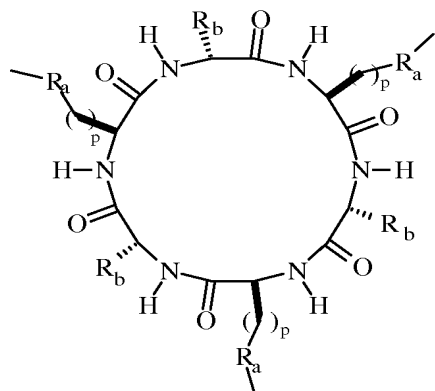
[[*]] m and m' are integers comprised from 1 to 5,

[[*]] V represents an -NH- or -CO- group forming an amide bond with X,

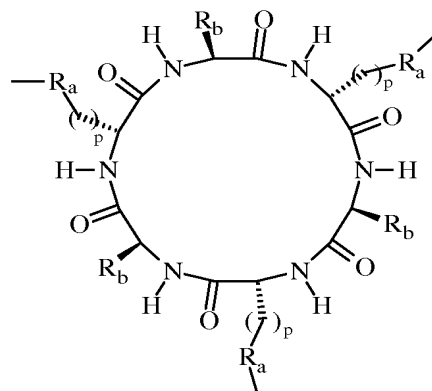
[[*]] Z represents an oxygen atom or a CH₂ group,

[[*]] Y represents either a nitrogen atom, or an R-C-group or an R-CONH-C- group, in which R can be an alkyl group with 1 to 10 carbon atoms, an alkenyl group with 1 to 10 carbon atoms, an alkynyl group with 1 to 10 carbon atoms, an aryl group with 5 to 12 carbon atoms, an aralkyl group with 5 to 14 carbon atoms or a heteroaryl group with 1 to 10 carbon atoms, said groups are capable of being non-substituted or substituted by 1 to 6 substituents chosen from the -COOH, -NH₂, -CONH₂ or alkoxy groups,

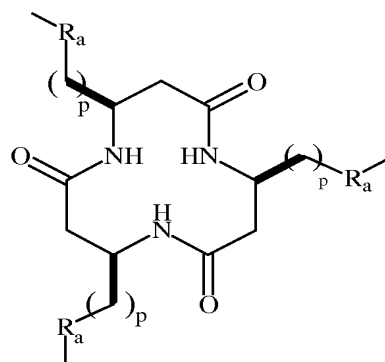
[[•]] or A is a cyclic C₃ radical corresponding to one of the following general formulae:



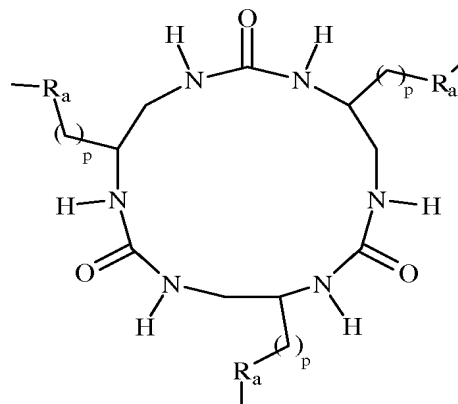
Ia



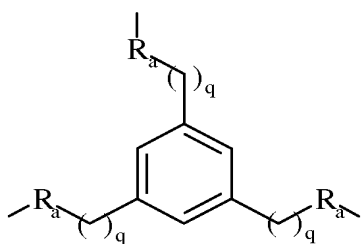
Ib



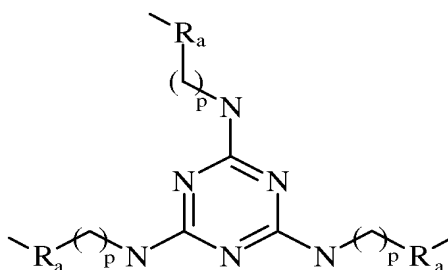
II



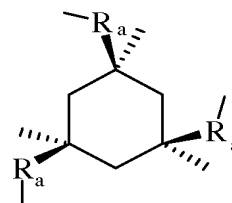
III



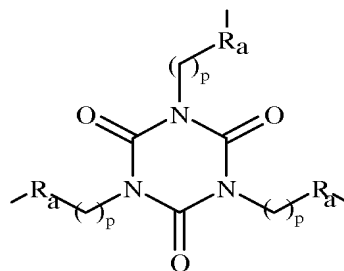
IV



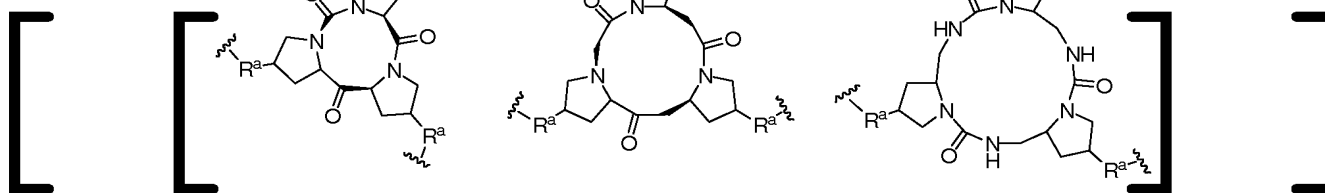
V



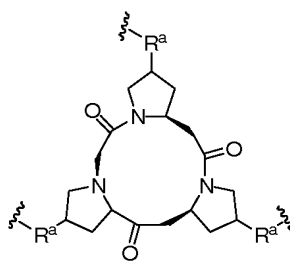
VI



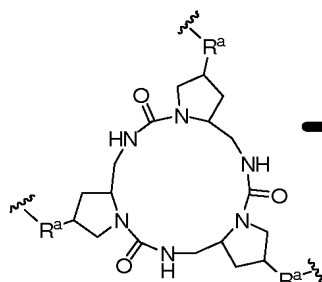
VIa



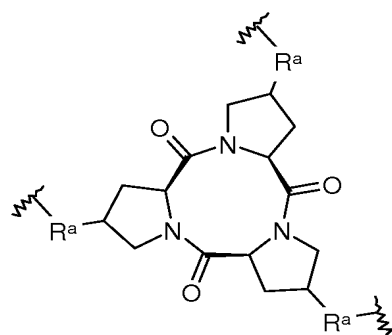
VIb



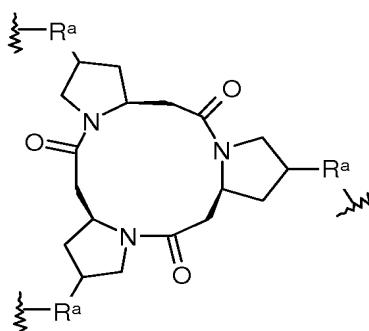
Vic



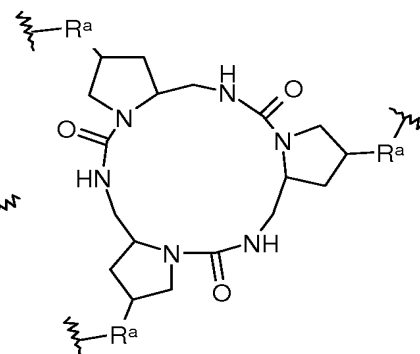
Vid



VIb



VIc



VIId

in which:

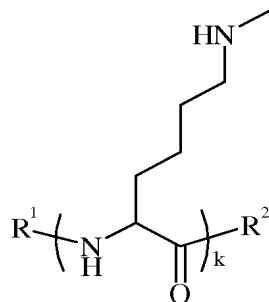
[[*]] R_a represents either an $-NH-$ group or a $-CO-$ group forming an amide bond with X,

[[*]] R_b represents the side chain of a proteinogenic amino acid,

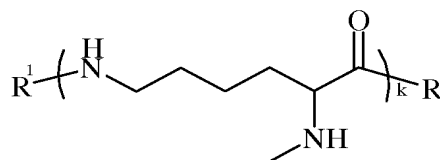
[[*]] p is an integer comprised from 1 to 4,

[[*]] q is an integer comprised from 0 to 4,

[[•]] or A is a non-symmetrical branched radical corresponding to the following general formulae:



VII



VIII

in which:

[[*]] k represents 3, 4, 5 or 6,

[[*]] R¹ represents either a hydrogen atom, or an amino acid residue chosen from the proteinogenic amino acids, or an RCO-, ROCO- or RNHCO- group, R being as defined above,

[[*]] R² represents either an -NH₂ group, or an -NHR group, or an amino acid residue chosen from the proteinogenic amino acids, R being as defined above,

[[-]] B corresponds to one of the following general

formulae: $\text{-R}^3\text{-Y-R}^4$ or $\begin{array}{c} \text{-R}^3\text{-Y-R}^4 \\ | \\ \text{R}^5 \end{array}$

in which:

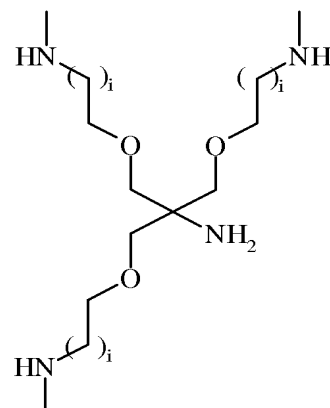
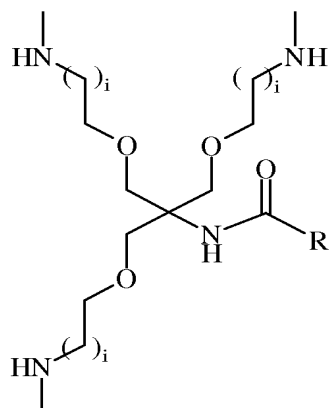
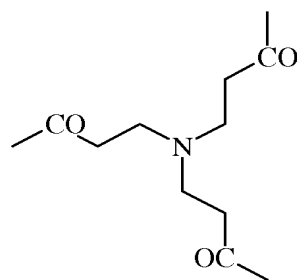
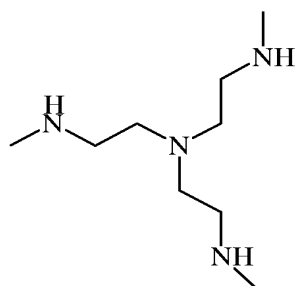
[[*]] Y represents a C₁-C₁₀ alkyl chain or an alkynyl or alkenyl or aryl or aralkyl or heteroaryl group,

[[*]] R³ represents either an -NH- group when V or R_a is a -CO- group, or a -CO- group when V or R_a is an -NH- group,

[[*]] R⁴ and R⁵ represent independently of one another a -CO- group or an -NH- group, and

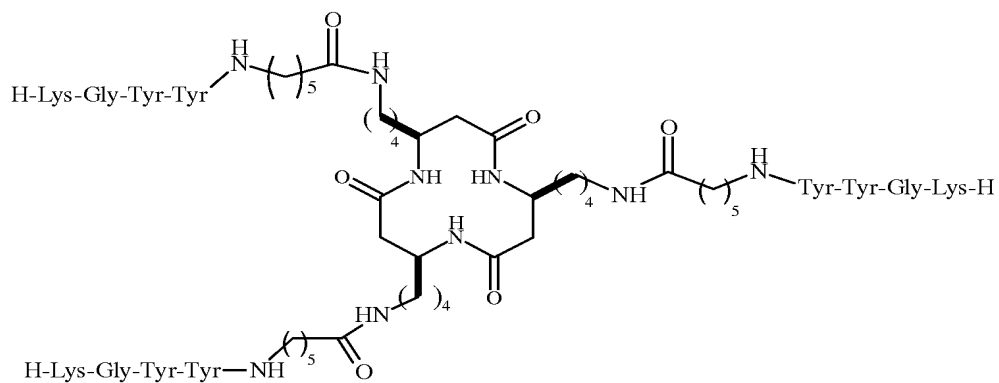
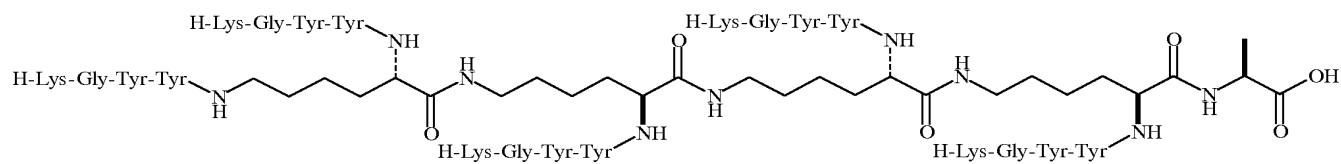
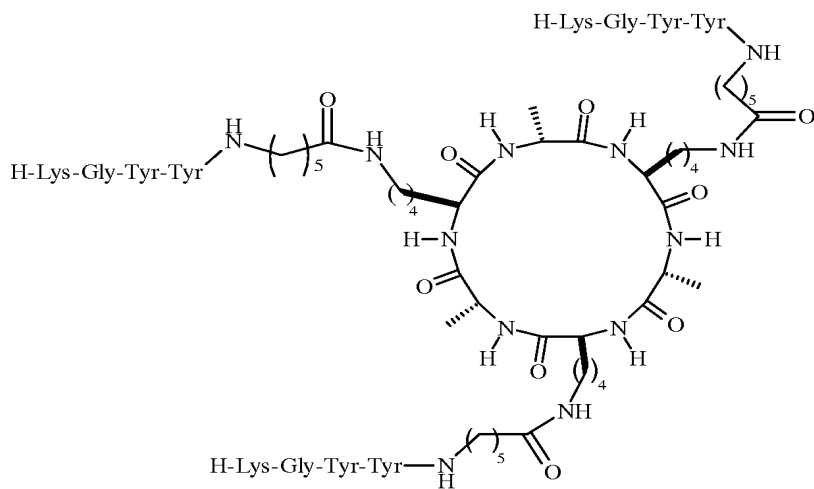
[[-]] -D and -D' are ~~peptides~~ each a peptide or pseudopeptide as defined in claim ~~1 or 2~~ 17.

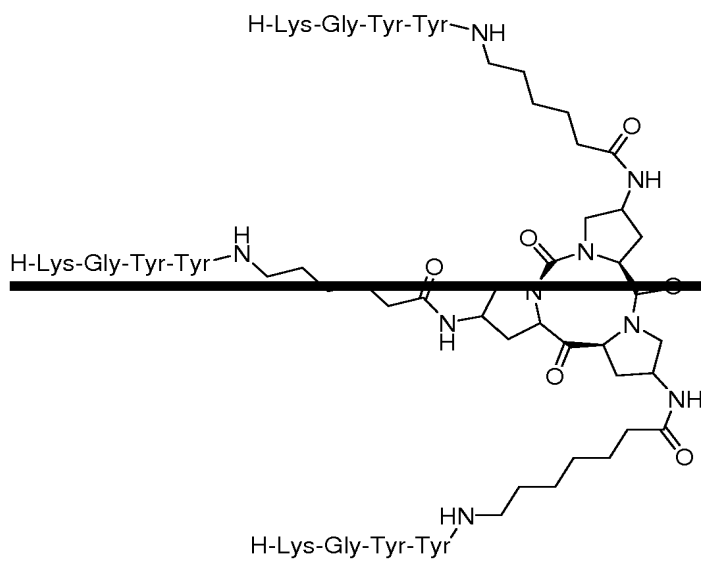
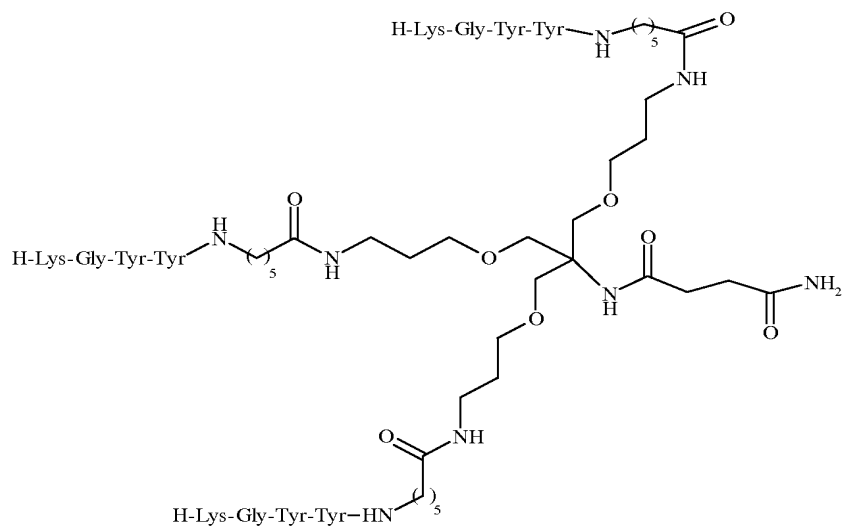
22. (Withdrawn) The molecule of claim 17, wherein
 A corresponds to one of the following formulae:

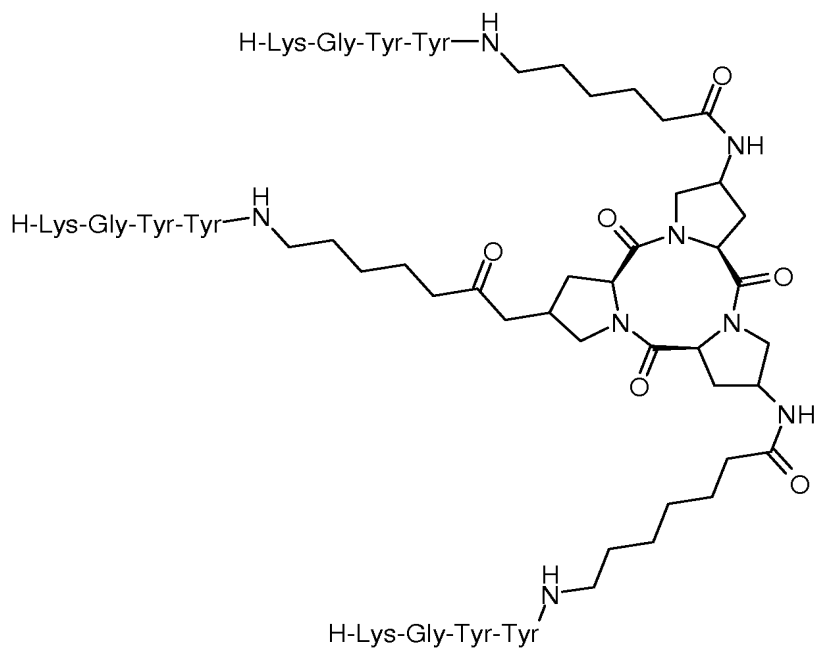
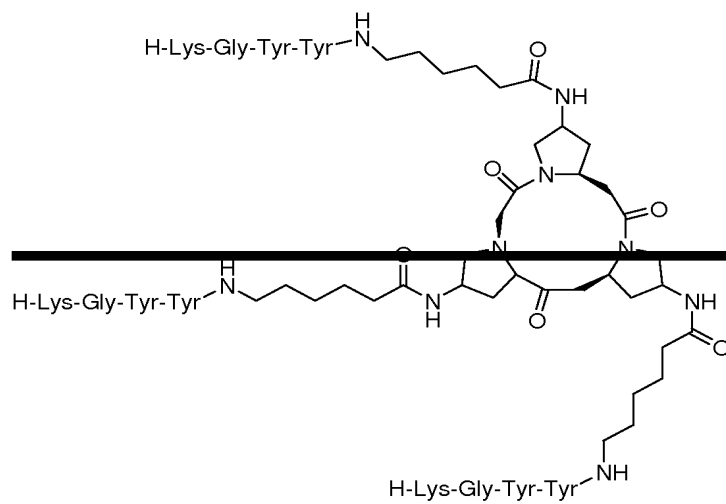


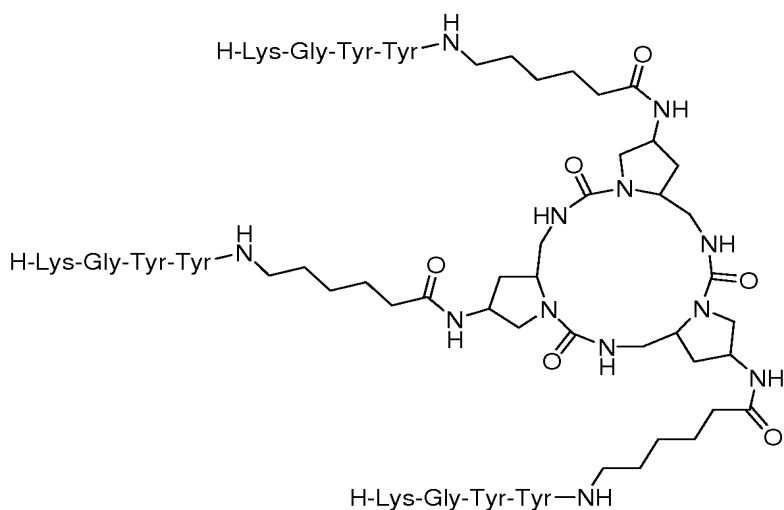
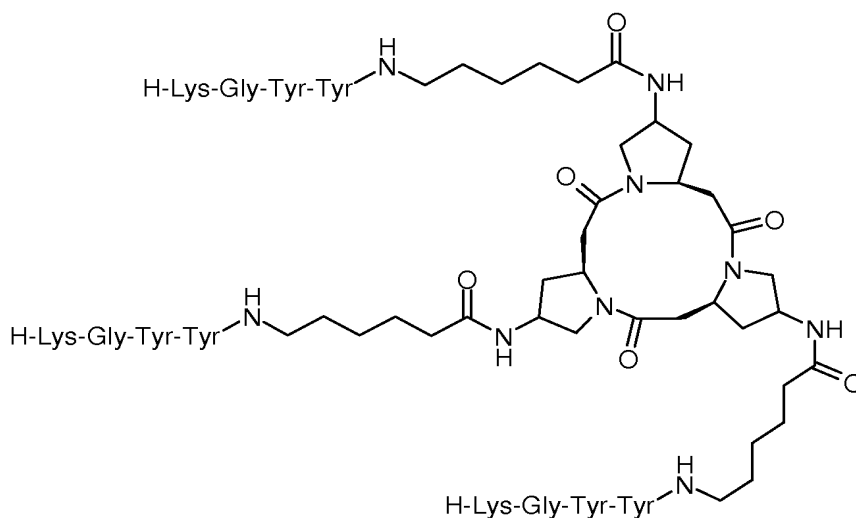
in which i represents an integer greater than or equal to 1.

23. (Currently Amended) The molecule of claim 17, of
 the following formula (peptide ~~sequences~~ sequence KGYG and ~~YYCK~~
 disclosed as SEQ ID NOS NO: 3 and ~~4~~, respectively):









24. (Currently Amended) A pharmaceutical composition ~~characterized in that it comprises~~ comprising, as active ingredient, a multimeric molecule according to claim 17, in combination with a pharmaceutically acceptable ~~vector~~ carrier.

25. (canceled)

26. (Withdrawn) A method of treatment of pathologies involving the inhibition or the activation of the immune response, with an effective amount of a multimeric molecule of claim 1.

27. (Withdrawn) The method of treatment according to claim 26, of pathologies involving the inhibition of the immune response, such as the rejection of grafts or auto-immune diseases.

28. (Withdrawn) The method of treatment according to claim 26, of pathologies involving the increase of immune response, such as cancers or parasitic, bacterial or viral infections.

29. (Withdrawn) A process for the preparation on a solid support of a multimeric molecule, in which A is a cyclic C₃ radical and corresponds to one of formulae Ia, Ib, II, VIb, VIc or VId as defined in claim 21, said process being characterized in that it comprises the following stages:

- the formation of a linear precursor of A, which precursor is constituted by an amino acid sequence forming a growing peptide chain, synthesized by successive coupling cycles

between residues of N-protected amino acids, three of which carry an R_a group of amine type, and the amine function of the growing peptide chain, and deprotection, the first amino acid residue being attached to a solid support,

- the cyclization of the abovementioned protected linear precursor of A,

- the cleavage of said protective groups, in order to release said protected amine functions,

- the coupling of the three released amine functions with an N-protected spacer arm B,

- the deprotection of the spacer arm B and the coupling of the amine functions released from the spacer arm B, with a D peptide already formed or formed in situ by the sequential assembly of the amino acid residues corresponding to the D peptide, and

- the cleavage of the molecule from the solid support, after the deletion of all the protective groups present on the functionalized side chains of the D peptide, in order to obtain the multimeric molecule.

30. (Withdrawn) A process for the preparation in solution of a multimeric molecule, in which A is a cyclic C_3 radical and corresponds to one of formulae Ia, Ib, II, VIb, VIc or VId as defined in claim 21, said process being characterized in that it comprises the following stages:

- the formation of a linear precursor of A, which precursor is constituted by an amino acid sequence forming a growing peptide chain, synthesized by successive coupling cycles between N-protected amino acid residues, three of which carry an amine-type R_a group, and the amine function of the growing peptide chain, and deprotection,

- the cyclization of the abovementioned protected linear precursor of A,

- the cleavage of said protective groups, in order to release said protected amine functions,

- the coupling of the three released amine functions with a -D-B peptide corresponding to a spacer arm B linked to a protected D peptide,

- the deprotection of the protective groups present on the D peptide, in order to obtain the multimeric molecule as defined in claim 1.

31.(Withdrawn) A process for the preparation of a multimeric molecule, in which A is a branched C_3 radical and corresponds to one of formulae IV, V, VI or VIa as defined in claim 21, said process being characterized in that it comprises the following stages:

- the coupling of the three amine functions of the radical A of formula IV, V, VI or VIa with a protected spacer arm B,

- the deprotection of the spacer arm B,

- the assembly of the deprotected spacer arm B with protected amino acids involved in the constitution of a D peptide, by successive cycles of coupling, purification and deprotection of the abovementioned amino acids,

- the deprotection of the last amino acid involved in the constitution of the D peptide, in order to obtain the multimeric molecule as defined in claim 1.

32. (Withdrawn) A process for the preparation on a solid support of a multimeric molecule, in which A is a non-symmetrical branched radical corresponding to one of formulae VII or VIII as defined in claim 21, said process being characterized in that it comprises the following stages:

- the grafting of a lysine onto a solid support, each of the two amino functions of the lysine, in positions α and ϵ respectively, being protected by different and orthogonal protective groups respectively,

- the extension of the peptide chain formed from the lysine, to the desired length, with successive couplings and deprotections

- *either of the amine functions in position α only, in order to obtain the radical A of formula VII, with protected amine functions in position ϵ ,

- * or of the amine functions in position ϵ only, in order to obtain the radical A of formula VIII, with protected amine functions in position α ,
- the coupling of the deprotected amino functions in position ϵ in the radical A of formula VII or in α position in the radical A of formula VIII, with a protected arm B,
- the assembly of the deprotected spacer arm B with a D peptide already formed or formed in situ by the sequential assembly of the amino acid residues corresponding to the D peptide, and
- the cleavage of the molecule thus obtained from the solid support, after the deletion of all the protective groups present on the functionalized side chains of the D peptide.

33. (New) The molecule of claim 17, wherein each peptide derived from the ligand of the human or murine CD40 receptor (CD40L) is chosen from the following:

Arg-Ile-Tyr-Tyr (SEQ ID NO: 22),

Arg-Ile-Tyr-Tyr-Gly-Lys (SEQ ID NO: 23),

or from fragments of said peptides,

the amino acids being equally able to be of L or D-configuration.